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Kinetics of Displacement Reactions Which Result in a Retention of Configuration

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KINETICS OF DISPLACEMENT REACTIONS WHICH RESULT IN A RETENTION OF CONFIGURATION

by

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By Victor Frank Mattson

Approved by H. F. Herbrandson

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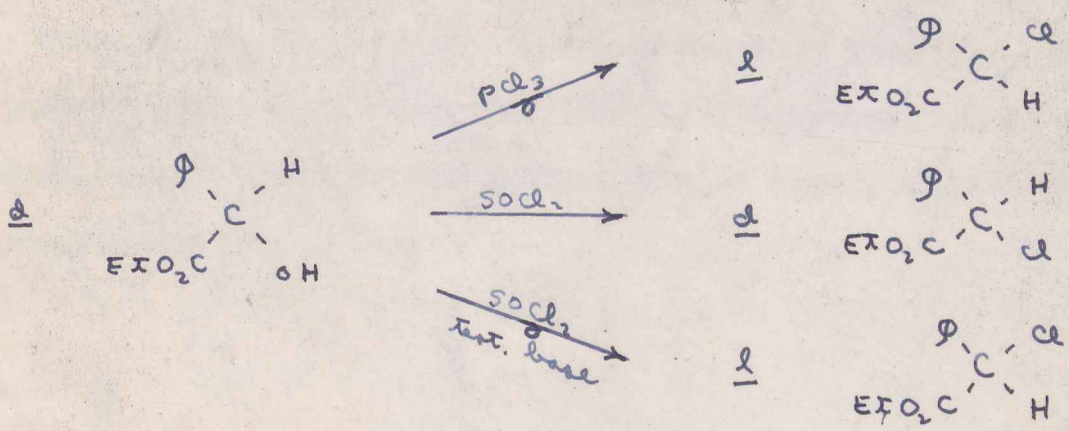
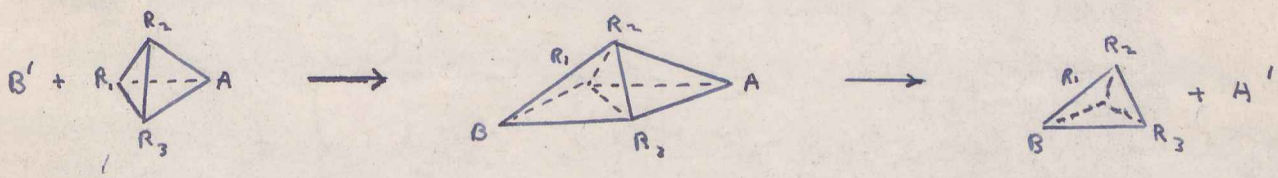
INTRODUCTION

Depending upon the halogenating agent and the reaction conditions d - ethyl mandelate may form either d - or l - ethyl phenylchloroacetate.



Situations of this type are common and have proven to be an interesting and a productive field for investigations into the mechanisms of organic substitution reactions.

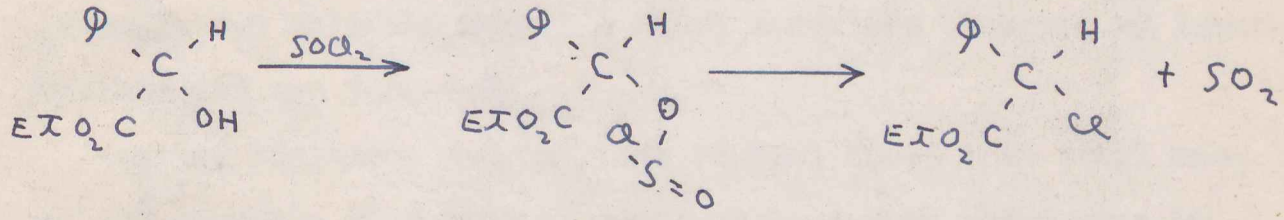
The inversion reaction (Walden Inversion) appears to be the more typical of the two and is also the more readily explained.



A and B ions have a repulsive effect upon each other and classical theory would demand that the ion B enter the molecule on the side opposite A. This displacement would of necessity result in an inversion of configuration.

The hypothesis that this simple type of substitution always involves an inversion has been substantiated by a good deal of theoretical and experimental work.

Substitutions which involve a retention of configuration must involve a fundamentally different mechanism. A frontal attack by the displacing ion would not seem feasible. A hypothesis that these reactions involve the formation of an intermediate and a subsequent intramolecular decomposition has received support.



This investigation was undertaken to obtain kinetic data on the decomposition of an intermediate of a retention type substitution.

HISTORICAL

The reactions between thionyl chloride and optically active hydroxy compounds were investigated by McKenzie, Clough, and Barrow (1,2,3). They showed that when the compound contained a phenyl group attached directly to the asymmetric carbon atom the resulting chloro-compound retained the same configuration as the parent compound. In contrast, with aliphatic compounds or with halogenating agents such as phosphorus trichloride or phosphorus pentachloride an inversion invariably occurred. They isolated an intermediate, amyl chlorosulfinate, which they decomposed (120°) to give amyl chloride. l - Phenylchloroacetate, b.p. 132.3° (15mm.), was obtained from l - ethyl mandelate although an intermediate was not isolated.

Kenyon, Lipscomb, and Phillips (4,5,6) found that ethyl mandelate showed a retention of configuration when acted upon by thionyl chloride alone but that it underwent an inversion when a tertiary base was also included. They offered the following conclusions:

1. Thionyl chloride and alcohols react to form chlorosulfinates.

2. The chlorosulfinates lose sulfur dioxide to form chlorides.

3. Tertiary bases aid this decomposition by forming unstable intermediates.

A tertiary base modifies only those reactions involving a phenyl group directly attached to the asymmetric carbon atom.

It was suggested that a retention of configuration will occur with halogenating agents which will form intermediates where the chlorine atom is still covalently held. A Walden inversion will take place if the chlorine enters the molecule as an anion. Tertiary bases, because they displace the chlorine as an anion, lead to an inversion.

More recent workers have endeavered to offer more detailed explanations. Cowdrey, Hughes, Ingold, Masterman and Scott (7) point out that the chlorosulfinate intermediate may ionize with the decomposition then involving an inversion. This reaction could be either an unimolecular or a dimolecular substitution. However the chlorosulfinate may instead undergo an intramolecular nucleophilic change which would show a complete retention of configuration. This unimolecular rearrangement would be expected to follow a first order reaction rate. This internal rearrangement is apparently possible only when an adjacent phenyl group has weakened the carbon-oxygen bond.

Hughes, Ingold, and Whitefield (8) note that with all common substituting halogenating agents (phosphorus pentachloride, thionyl chloride, hydrogen chloride, phosphorus pentabromide) an inversion is produced unless there is present at the seat of substitution a sufficiently powerful electron-releasing group.

Choppin, together with Frediani, Kirby and Compere, has studied the kinetics of the decomposition of two chloroformates

(9,10,11). It was shown that ethyl chloroformate undergoes homogeneous, unimolecular decomposition between 150° and 195° and that carbon dioxide and ethyl chloride are the only products. A reaction rate constant was determined. Further work using an excess of carbon dioxide showed no measurable reversibility. A simple rearrangement mechanism was suggested.

In a similar investigation Choppin found that isopropyl chloroformate undergoes a homogeneous and first-order decomposition between 180° and 220°. In this case two simultaneous decomposition reactions occur. One gives isopropyl chloride and carbon dioxide; the other, propylene, hydrogen chloride and carbon dioxide.

There were no reports found in the literature of any work done with chlorosulfinates comparable with that of Choppin on chloroformates. Gerrard (12, 13, 14) has in recent years investigated a variety of chlorosulfinate compounds. He describes rather qualitatively the decompositions of phenyl chlorosulfinate and carbethoxybenzyl chlorosulfinate, alone and in the presence of sundry tertiary bases.

DISCUSSION

Ethyl mandelate chlorosulfinate has been postulated to be the intermediate formed in a retention type displacement reaction (5). A kinetic study of the decomposition of this intermediate was the specific object of this investigation.

The chlorosulfinate was readily prepared and purified. It could be decomposed at a convenient temperature with a convenient rate. The sulfur dioxide evolved made possible the employment of a simple and continous analytical method for following the reaction.

Considering the first-order reaction equation:

$$-\frac{dY}{dt} = kY$$

$$-\ln Y = kt + C$$

$$\log Y = -\left(\frac{k}{2.303}\right)t + C'$$

X = amount of sulfur dioxide evolved or chlorosulfinate reacted.
a = amount of the chlorosulfinate initially present.
Y = amount of the chlorosulfinate remaining at time t.
Y = (a - X)

The log Y vs. t plot for a true first-order reaction will thus give a straight line. The reaction rate constant is readily obtained from the slope of this line.

k = (-2.303) (slope)

It was found that small amounts of chloride were being evolved along with the sulfur dioxide. The source of this chloride was not apparent and the experimental support

necessary for any supposition was beyond the scope of this work.

Considering the positive curvature of the chloride vs. time curve (Figure 5), it does not seem feasible that this chloride came from any remaining traces of the thionyl chloride.

Possibly the chloride resulted from the volatilization and subsequent hydrolysis of the ethyl phenylchloroacetate. It was shown that this phenylchloroacetate was not rapidly hydrolyzed under alkaline conditions at room-temperature.

Regardless of its source the chloride was readily and directly corrected for.

The determination of the initial amount of the chlorosulfinate presented a more subtle problem.

In Runs I, II, and III the assumption was made that no appreciable decomposition occurred until the substance was heated to 30°. The initial chlorosulfinate was calculated from the weight of the ethyl mandelate used in its preparation. The three runs, conducted under identical conditions, gave reaction rate constants which were in good agreement. This reproducibility would seem to attest to the validity of the experimental methods used in following the reaction. In all cases, however, the first-order curves showed S-shape characteristics (Figures 2 and 3). This fact, together with the probability that an appreciable amount of the chlorosulfinate did decompose during the preliminary work, suggested a need

for a more accurate determination of the initial amount of the material.

In Run IV an attempt was made to determine the initial chlorosulfinate by hydrolyzing an aliquot sample of the starting solution and measuring the chloride formed with a Volhard titration. This hydrolysis had to be carried out in a manner which had been shown not to hydrolyze the chloroacetate. For that reason the sample could not be heated to rid it of sulfur dioxide. Apparently the sulfite ion precipitated as silver sulfite since the silver nitrate required in the titration was equivalent to slightly less than three times the maximum possible amount of chloride. An assumption was made that the silver sulfite was precipitated quantitatively. These data indicated that the chlorosulfinate decomposed to the extent of about eight per cent during the preliminary treatment.

First-order curves were drawn (Figure 4) and the rate constants were calculated using values of the initial chlorosulfinate determined by each of the two methods. The constants differed by about 18%. Both of these values were considerably higher than in the first three runs. The fact that in both of the curves drawn for Run IV the points follow a straight line more closely than do the points in any of the first three runs, suggests that the values of the reaction rate constant are probably somewhat low in Runs I, II, and III.

Of the two curves obtained in Run IV the one resulting from the hydrolysis method of determining initial chlorosulfinate is the better. The corresponding constant is, therefore, probally more accurate.

Additional work to justify the hydrolysis procedure and to confirm the reaction rate constant obtained in Run IV would be in order. This is not possible at the present time. Nevertheless several conclusions can be drawn from the results of this investigation.

1. The decomposition of ethyl mandelate chlorosulfinate proceeds with a first-order rate.
2. The reaction rate constant is of the order of 1.8×10^{-4} sec.$^{-1}$
3. The postulate that the retention type displacement reaction involves the intremolecular decomposition of an intermediate is strengthened.

EXPERIMENTAL

Preparation of Ethyl Mandelate

Ethyl mandelate was prepared by refluxing for five hours 68 gm. of dl - mandelic acid, 500 ml. of 99.5 per cent ethyl alcohol, and 25 ml. of concentrated sulfuric acid. After neutralization with sodium carbonate a portion of the excess alcohol was removed by distillation and the ester was extracted with ethyl ether. The ether was removed and the ester was purified by a vacuum distillation, b.p. 101° (1.7 mm.), (15).

Preparation of Ethyl Mandelate Chlorosulfinate

Ethyl mandelate chlorosulfinate was prepared by reacting ethyl mandelate (0.040 m.) with an excess of thionyl chloride (0.1 m.). The excess thionyl chloride was necessary if the chlorosulfinate and not the sulfite ester was to be obtained (16). Unreacted ethyl mandelate would also interfere.

The ester was added to the thionyl chloride contained in a 125 ml. round-bottom flask and cooled in an ice-bath. This flask was equipped with a gas delivery tube leading to its bottom and with a ground-glass exit tube at its neck. Dry nitrogen was slowly bubbled through the flask to agitate the mixture and to remove the hydrogen chloride formed. Immediately after mixing, the flask was removed from the bath and allowed to come to room temperature. The reaction was allowed to proceed for three hours after which time 150 ml. of dry toluene

was added. The mixture was then placed in a refrigerator overnight.

Toluene was used as a solvent in all of the work. Because of its nonpolar nature it was felt that it would not significantly effect the reaction mechanism (17). It was also readily obtainable in sufficiently pure condition.

The next day the excess thionyl chloride was removed under diminished pressure. The solutions remained on the aspirator for about one and one-half hours at room temperature and for twenty minutes at 30°. About 50 ml. of toluene and thionyl chloride was distilled during this period.

This preparation was at all times protected from atmospheric moisture with calcium chloride drying tubes. The nitrogen was passed through a potassium hydroxide U-tube and a drying tube filled with calcium chloride and "Drierite".

Decomposition of Ethyl Mandelate Chlorosulfinate

The reaction was followed continuously by employing the apparatus shown in Figure 1.

The decomposition was carried out in the same flask as the preparation. This flask was immersed in a soy-bean oil bath equipped with a mercury thermoregulator. The temperature was maintained at 80.1 ± 0.3°.

Nitrogen was used to carry the sulfur dioxide through the system. It also served to prevent oxidation of sulfite to sulfate.

The gases were led to the titration beaker through a scintered glass bubbler which produced excellent dispersion and which caused sufficient agitation of the absorbing solution so that further stirring seemed unnecessary.

The rate of nitrogen flow was indicated by a capillary-tube flowmeter. Ethylene glycol was used in the manometer. The instrument was calibrated by measuring the time required for nitrogen to displace measured volumes of water. During each run the flow rate was kept constant by making the necessary adjustments on the cylinder valve.

The sulfurous acid formed by the absorbed sulfur dioxide was titrated as a monobasic acid (to pH of 4.4) (18). A color indicator (methyl orange) was used in some preliminary work but the sulfite buffering action led to unsatisfactory results. A Beckman glass electrode pH meter was found to serve well.

Increments of sodium hydroxide solution were added to the titration beaker from a burette and the times required for neutralization were measured. In all runs the titration vessel initially contained 150 ml. of water.

The chloride evolved was corrected for by withdrawing aliquot samples from the titration beaker from time to time and determining the amount of chloride by Volhard's method. All samples were removed when the solution was at the equivalence point. Specific chloride values were obtained from a chloride vs. time curve drawn for each run (Figure 5).

It should be understood that the initial time value was entirely arbitrary and that the time readings have only a relative value. The initial time cannot be absolute because of the varibles involved in bringing the solution up to 80° and in establishing the gas flow. The first-order reaction equation does not require absolute measurements.

Ethyl Phenylchloroacetate

The ethyl phenylchloroacetate formed in Runs I and II was isolated and purified by a vacuum distillation. The boiling point was 83.4° (1.7 mm.). McKenzie and Barrow (2) reported 138-3° (15 mm.).

An alkaline hydrolysis of this material at room temperature was attempted. Three grams of the phenylchloroacetate was shaken with 50 ml. of 0.13 N. sodium hydroxide for fifteen minutes. A Volhard titration showed less than one per cent hydrolyzed.

A second hydrolysis was performed under similar conditions except that the alkaline mixture was boiled and shaken. In this case twenty-five per cent of the ethyl phenylchloroacetate was hydrolyxed.

Determination of Initial Chlorosulfinate

Immediately before beginning Run IV the toluene solution was weighed. A small amount (3 ml.) was withdrawn and weighed. This aliquot sample was hydrolyxed at room temperature with

50 ml. of 0.13 N. sodium hydroxide. A modified Volhard titration was used to determine the chloride (19).

To the hydrolysis mixture was added: 10 ml. 6 N. nitric acid, 50 ml. glacial acetic acid, 25 ml. chloroform, and 25 ml. 0.1 N. silver nitrate. The titration was performed with 0.1 N. potassium thiocyanate using ferric ion indicator.

The total solution was found to be equivalent to 0.1112 moles of silver nitrate. Only 0.03935 moles of ethyl mandelate were used in preparing the ethyl mandelate chlorosulfinate.

Reagents

Eastman Kodak "White Label" dl-mandelic acid was used.

The "Reagent" grade toluene was dehydrated by distillation.

TABLE I

DECOMPOSITION OF ETHYL MANDELATE CHLOROSULFINATE RUN I

sodium hydroxide moles X 10^3	chloride	X	Y	log Y	time seconds
1.93	0.30	1.63	35.86	1.554	550
3.86	0.50	3.36	34.07	1.532	1005
5.78	0.68	5.10	32.33	1.510	1410
7.72	0.83	6.90	30.53	1.485	1820
9.65	1.00	8.65	28.78	1.459	2245
11.58	1.14	10.44	26.99	1.431	2725
13.52	1.30	12.22	25.21	1.402	3234
15.43	1.46	13.97	23.46	1.370	3805
17.36	1.64	15.72	21.71	1.337	4423
19.30	1.85	17.45	19.98	1.301	5120
21.25	2.08	19.17	18.26	1.262	5949
23.18	2.37	20.81	16.62	1.221	6887
25.18	2.63	22.55	14.88	1.173	7919
27.02	2.85	24.17	13.26	1.123	9021
28.30	2.98	25.28	12.15	1.085	9838
29.60	3.07	26.53	10.90	1.037	10641
30.87	3.15	27.72	9.71	0.987	11541
32.16	3.23	28.93	8.50	0.929	12581
33.47	3.34	30.13	7.30	0.863	13724

moles of ethyl mandelate 0.0376

nitrogen flow-rate 0.063 liter/minute

REACTION RATE CONSTANT 1.21×10^{-4} $sec.^{-1}$

TABLE II

DECOMPOSITION OF ETHYL MANDELATE CHLOROSULFINATE RUN II

sodium hydroxide moles X 10^3	chloride ion	X	Y	log Y	time seconds
1.93	0.12	1.81	37.51	1.547	262
3.86	0.21	3.65	35.67	1.552	554
5.78	0.37	5.41	33.91	1.530	873
7.72	0.50	7.22	32.10	1.507	1177
9.65	0.63	9.02	30.30	1.481	1523
11.58	0.77	10.81	28.51	1.455	1886
13.52	0.91	12.61	26.71	1.427	2280
15.43	1.04	14.39	24.93	1.397	2708
17.38	1.20	16.18	23.14	1.364	3187
19.30	1.37	17.93	21.39	1.330	3719
21.25	1.48	19.77	19.55	1.291	4344
23.18	1.71	21.47	17.85	1.252	5088
25.18	1.90	23.28	16.04	1.205	5966
27.02	2.10	24.92	14.40	1.158	7059
27.99	2.20	25.79	13.53	1.131	7656
28.85	2.25	26.60	12.72	1.104	8320
29.92	2.40	27.52	11.80	1.072	9037
30.87	2.50	28.37	10.95	1.039	9802
31.85	2.58	29.27	10.05	1.003	10592
32.81	2.72	30.09	9.23	0.965	11431
33.47	2.82	30.65	8.67	0.938	12002
34.12	2.90	31.22	8.10	0.908	12585
34.78	3.00	31.78	7.54	0.877	13169
35.39	3.08	32.31	7.01	0.846	13759
36.04	3.17	32.87	6.45	0.810	14387
36.68	3.26	33.42	5.90	0.771	15006
37.32	3.32	34.00	5.32	0.726	15603
38.60	3.51	35.09	4.23	0.626	16863
39.86	3.70	36.16	3.16	0.500	18147

moles of ethyl mandelate 0.0393

nitrogen flow-rate 0.055 liter/minute

REACTION RATE CONSTANT 1.21×10^{-4} $sec.^{-1}$

TABLE III

DECOMPOSITION OF ETHYL MANDELATE CHLOROSULFINATE RUN III

sodium hydroxide moles X 10^3	chloride ion	X	Y	log Y	time seconds
2.57	0.43	2.14	38.24	1.583	105
3.22	0.48	2.74	37.64	1.576	200
3.86	0.51	3.35	37.03	1.569	293
5.15	0.65	4.50	35.88	1.555	496
7.08	0.80	6.28	34.10	1.533	782
8.36	0.90	7.46	32.92	1.517	981
10.29	1.04	9.25	31.13	1.493	1294
12.23	1.23	11.00	29.38	1.468	1648
14.16	1.46	12.70	27.68	1.442	2048
16.08	1.61	14.47	25.91	1.413	2409
18.02	1.87	16.15	24.23	1.384	2822
19.94	2.10	17.84	22.54	1.353	3281
21.87	2.37	19.50	20.88	1.320	3778
23.80	2.66	21.14	19.24	1.284	4327
25.73	3.02	22.71	17.67	1.247	4955
27.67	3.41	24.26	16.12	1.207	5636
29.60	3.93	25.67	14.71	1.168	6536
32.15	4.65	27.50	12.88	1.110	7793
33.46	5.03	28.43	11.95	1.077	8432
34.15	5.40	29.35	11.03	1.043	9008
36.02	6.00	30.02	10.36	1.015	9854
37.98	6.88	31.08	9.30	0.968	10942
39.23	7.50	31.73	8.65	0.937	11666
40.53	8.42	32.11	8.27	0.918	12516

moles of ethyl mandelate 0.0404

nitrogen flow-rate 0.051 liter/minute

REACTION RATE CONSTANT 1.26×10^{-4} $sec.^{-1}$

TABLE IV

DECOMPOSITION OF ETHYL MANDELATE CHLOROSULFINATE RUN IV

sodium hydroxide moles X 10^3	chloride ion	X	Y	log Y	time seconds
1.04	0.59	0.45	38.90	1.590	745
1.56	0.60	0.94	38.41	1.584	886
2.08	0.63	1.45	37.90	1.579	1025
3.13	0.68	2.45	36.90	1.567	1255
4.17.	0.71	3.46	35.89	1.555	1485
5.22	0.78	4.44	34.91	1.543	1705
6.26	0.82	5.44	33.91	1.530	1915
7.30	0.91	6.39	32.96	1.518	2090
8.86	0.97	7.89	31.46	1.500	2386
10.96	1.09	9.87	29.48	1.470	2786
12.00	1.20	10.80	28.55	1.456	3031
13.58	1.39	12.19	27.16	1.434	3436
15.12	1.48	13.64	25.71	1.410	3698
16.69	1.67	15.02	24.33	1.386	4073
18.25	1.87	16.38	22.97	1.361	4432
19.81	2.10	17.71	21.64	1.335	4798
21.38	2.32	19.06	20.29	1.307	5184
22.95	2.60	20.35	19.00	1.279	5572
24.52	2.96	21.56	17.79	1.250	6028
26.60	3.38	23.22	16.13	1.208	6690
28.18	3.76	24.42	14.93	1.174	7242
29.73	4.12	25.61	13.74	1.138	7759
31.28	4.53	26.75	12.60	1.100	8379
32.84	5.01	27.83	11.52	1.061	9009
34.93	5.60	29.33	10.02	1.001	9982

moles of ethyl mandelate 0.03935

nitrogen flow-rate 0.056 liter/minute

REACTION RATE CONSTANT 1.50×10^{-4} $sec.^{-1}$

TABLE V

DECOMPOSITION OF ETHYL MANDELATE CHLOROSULFINATE RUN IV

Calculations made using the value of initial chlorosulfinate as determined by the hydrolysis method.

Y moles X 10^{3}	log Y	time seconds
35.68	1.552	745
35.19	1.546	886
34.68	1.540	1025
33.68	1.527	1255
32.67	1.514	1485
31.69	1.500	1705
30.69	1.487	1915
29.74	1.473	2090
28.24	1.451	2386
26.26	1.419	2788
25.33	1.404	3031
23.94	1.379	3436
22.49	1.352	3698
21.11	1.324	4073
19.75	1.296	4432
18.42	1.265	4798
17.07	1.232	5184
15.78	1.198	5572
14.57	1.163	6028
12.91	1.111	6690
11.71	1.069	7242
10.52	1.022	7759
9.38	0.972	8379
8.30	0.919	9008
6.80	0.833	9982

initial chlorosulfinate 0.03613 moles X 10

REACTION RATE CONSTANT 1.82×10^{-4} $sec.^{-1}$

TABLE VI

CHLORIDE ION CORRECTION DATA

RUN I

total chloride ion $mX10^3$	time sec.
0.66	1005
1.09	1685
1.23	2725
1.86	4860
2.85	7242
3.48	10641

RUN II

total chloride ion $mX10^3$	time sec.
0.21	554
0.91	2280
1.48	4344
2.25	8320
2.58	10592

RUN III

total chloride ion $mX10^3$	time sec.
0.65	496
1.61	2409
5.03	8432
8.42	12516

RUN V

total chloride ion $mX10^3$	time sec.
0.91	2090
1.39	3436
2.96	6028
5.01	9008

FIGURE 1

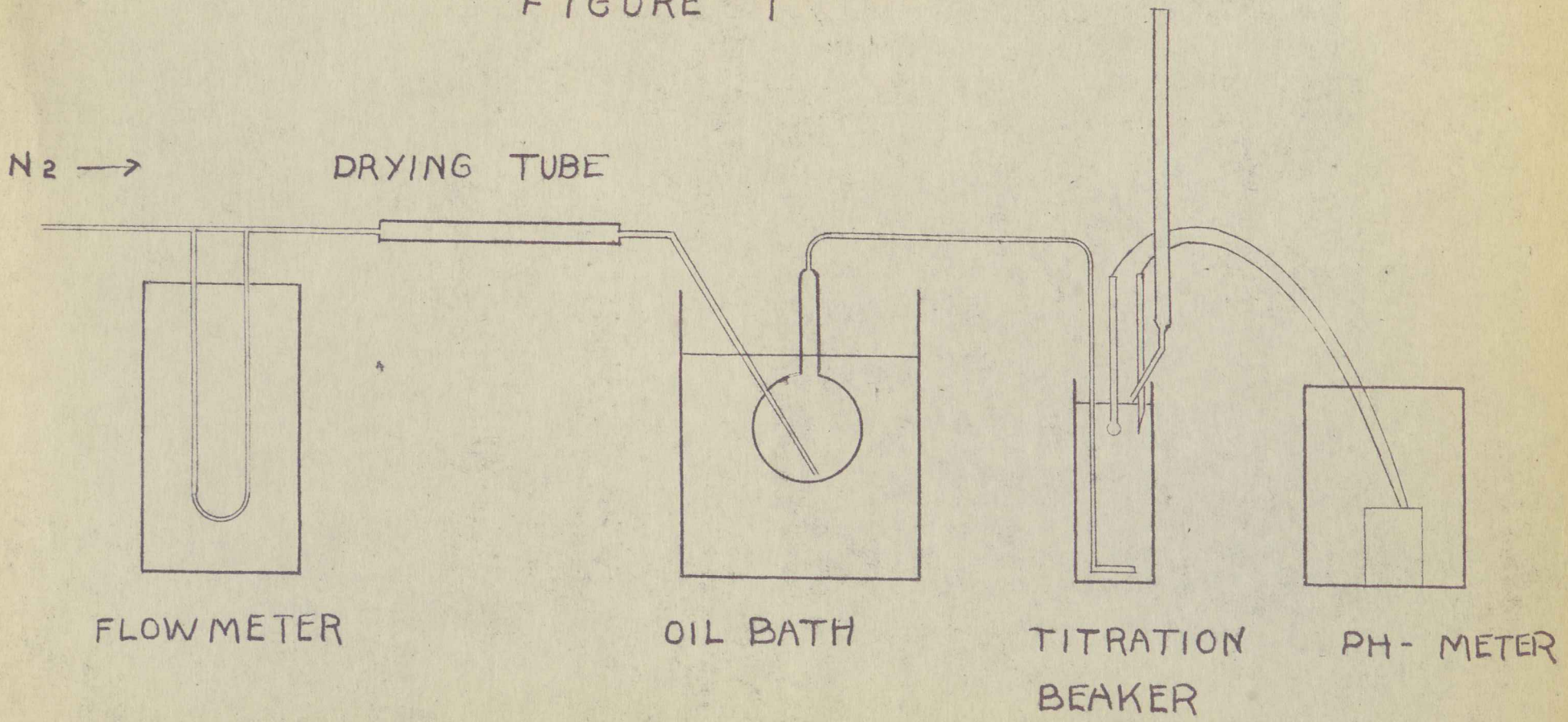

N2 ⟶
DRYING TUBE
FLOW METER
OIL BATH
TITRATION BEAKER
PH- METER

FIGURE 2A

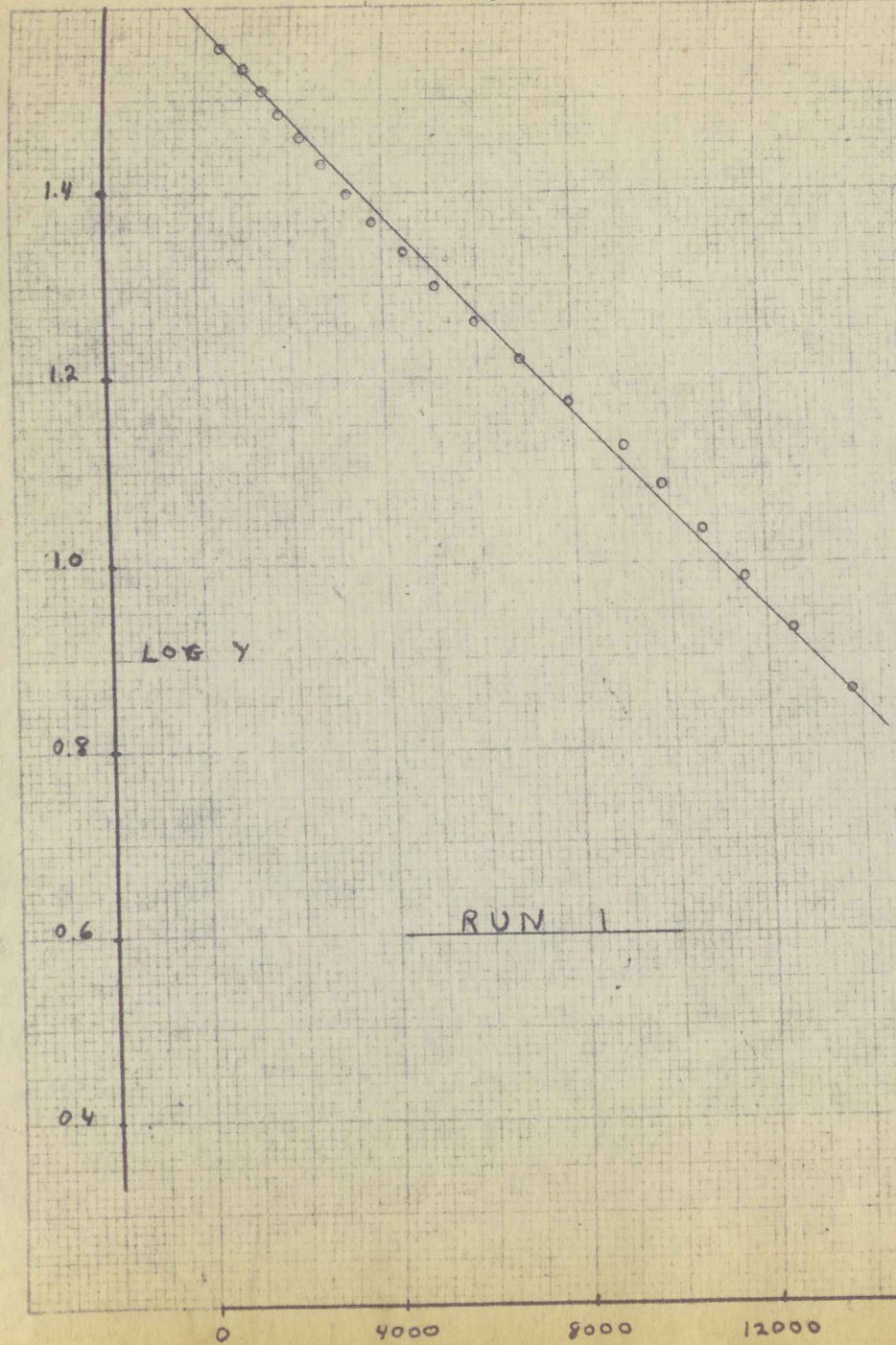


FIGURE 2B

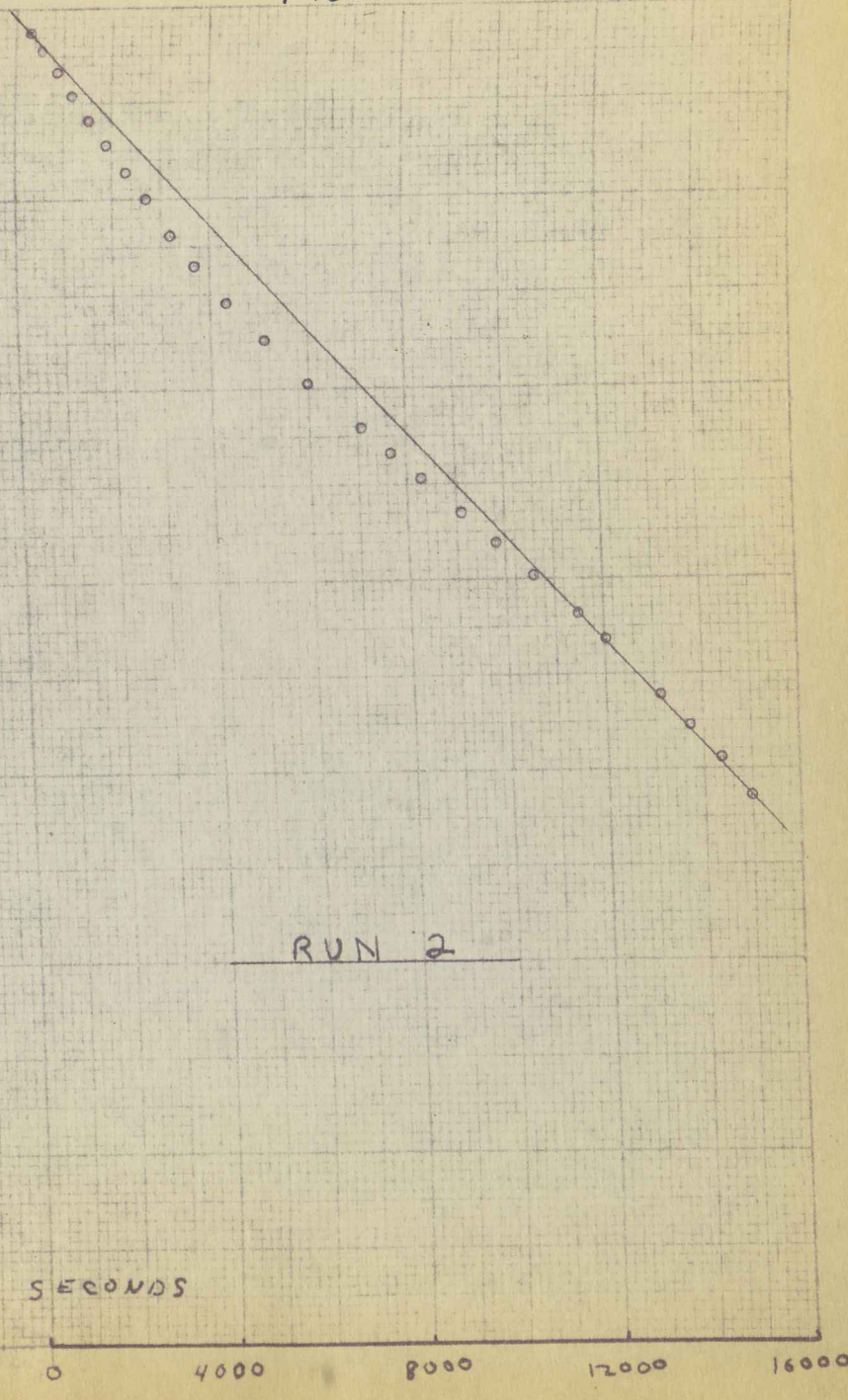
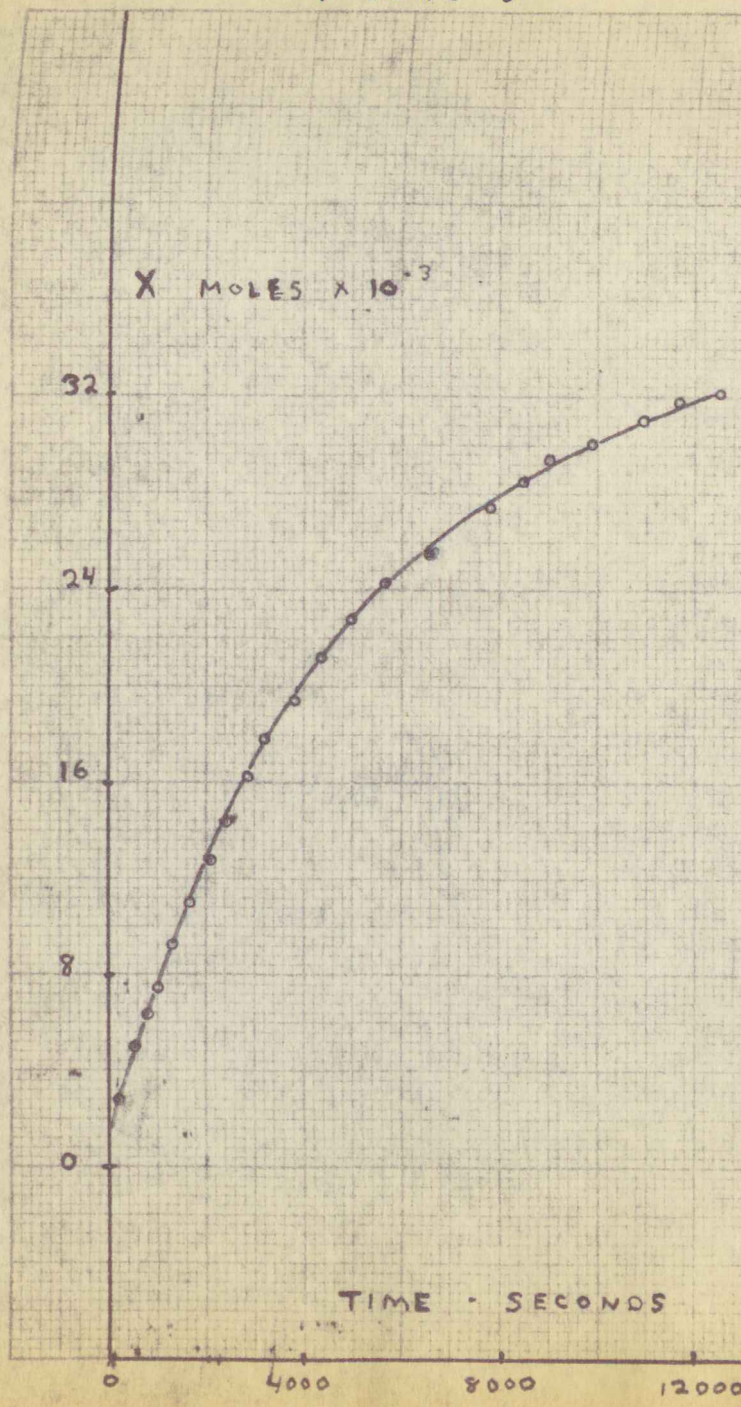


FIGURE 3A



RUN 3

FIGURE 3B

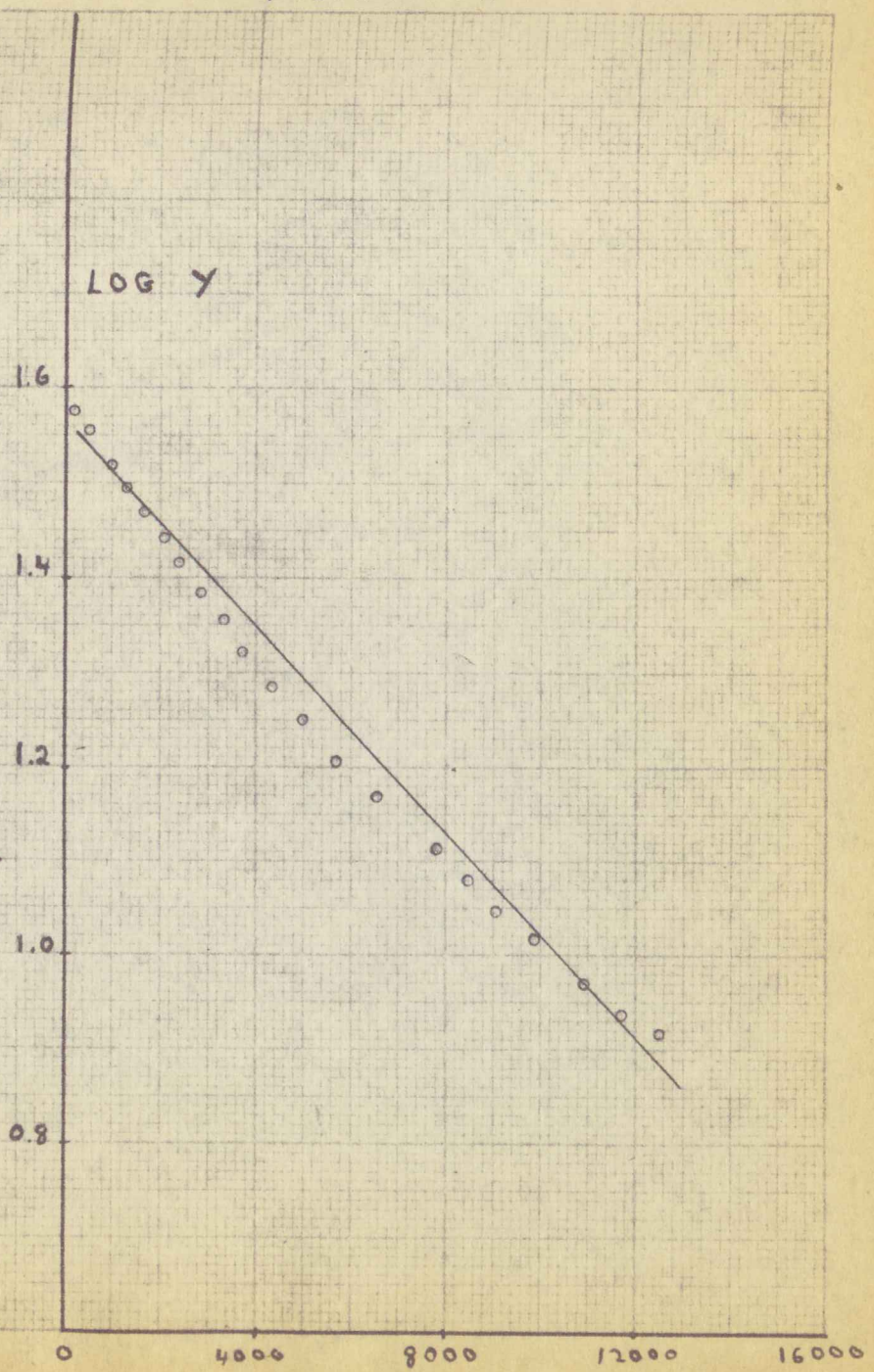
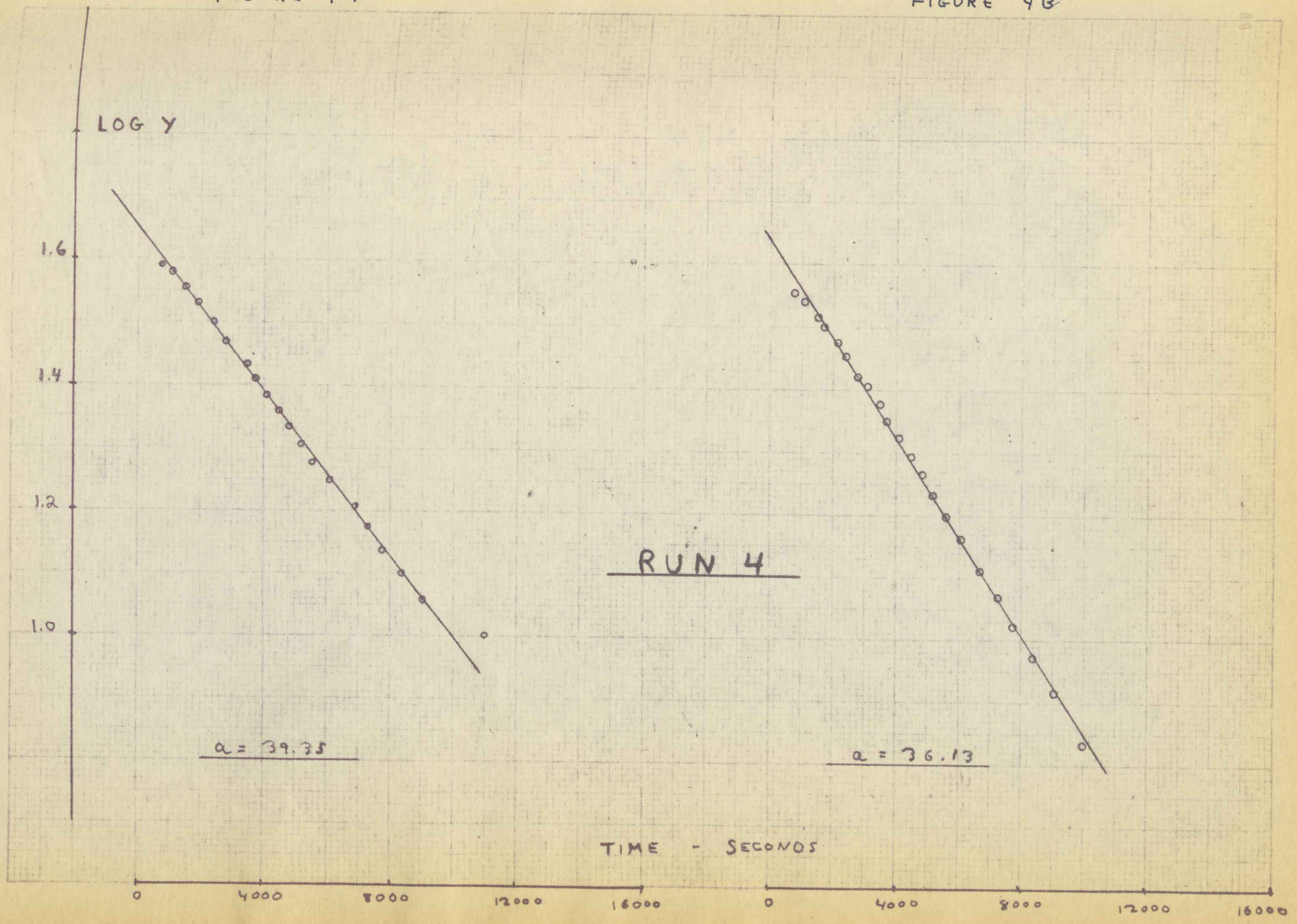
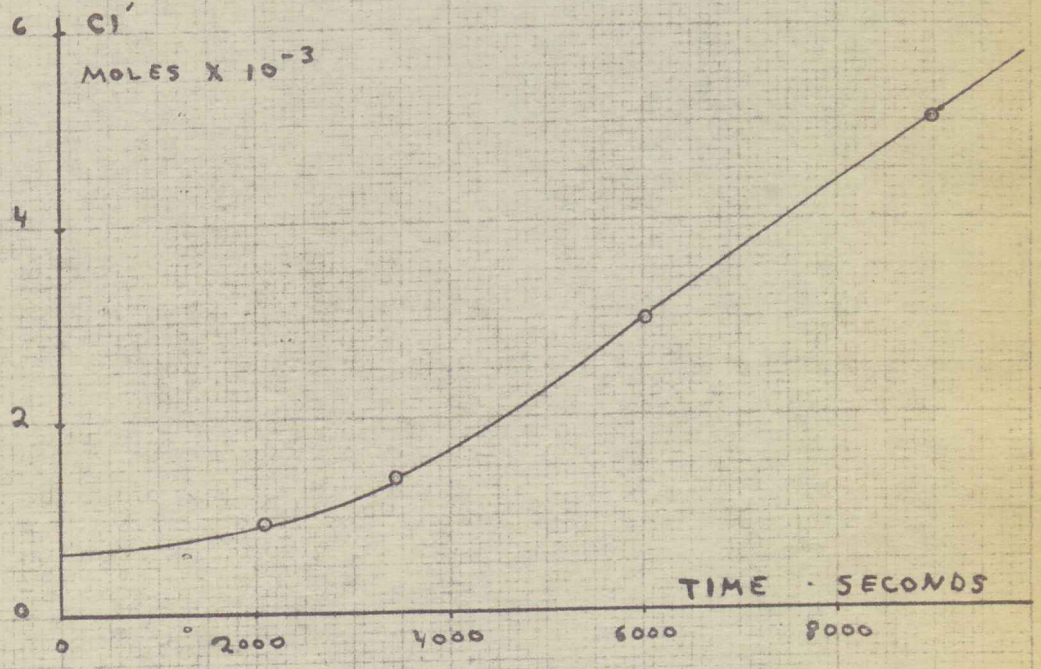


FIGURE 4A

FIGURE 4B





RUN 4

CHLORIDE CORRECTION

FIGURE 5

SUMMARY

A kinetic study was made of the decomposition of ethyl mandelate chlorosulfinate. This decomposition was followed by measuring the rate of evolution of sulfur dioxide.

The decomposition was found to be a first-order reaction with a reaction rate constant of about 1.8×10^{-4} sec.$^{-1}$ at 80.1 0.3°.

This work suggests that displacement reactions which result in a retention of configuration involve the intramolecular decomposition of an intermediate product.

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